

# A BRIEF INSIGHT INTO STIMULANTS' EFFECTS: A REVIEW BASED ON STUDENTS

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## ABSTRACT

Central nervous system stimulants of various levels of effectiveness are commonly used among students worldwide. These stimulants are a group of drugs that increase vigilance, alertness, and excitation. In the present study, three stimulants; caffeine, methylphenidate, and modafinil are compared in terms of their mechanisms of action, effects on memory, and addiction, especially in the younger population. Caffeine is the most widely used stimulant after methylphenidate and modafinil. Although the possibility of addiction due to caffeine is highly dose-dependent, there is a potential for abuse of methylphenidate and modafinil. These stimulants are used for a variety of reasons, such as staying awake to study, increasing alertness to complete assignments, or for recreational purposes among students. Also, since many stimulants are readily accessible to many individuals, such substances may be misused. The aim of the study is to show different aspects of caffeine, methylphenidate, and modafinil use on epidemiology, mechanism, addiction, and effect on electroencephalogram and long-term memory.

**Keywords:** Caffeine, methylphenidate, modafinil, attention, ADHD

## INTRODUCTION

In circadian rhythm, the cortex moves around two states: Wakefulness and sleep (1). Wakefulness indicates an aroused state of mind (2). This arousal can either be achieved physiologically by the hypothalamus and reticular activating system or through certain central nervous system (CNS) stimulants (3). CNS stimulants are a group of drugs that increase vigilance, alertness, and excitation (4). Several compounds can be listed, but a few of them are more popular than others. One such compound is caffeine, which is found especially in coffee (5). Other chemicals that are classified as drugs can be used legally or illegally for many purposes, one of them being attention deficit hyperactivity disorder (ADHD) (6).

Despite their benefits in the treatment of disorders such as ADHD and narcolepsy, modafinil and methylphenidate can be misused due to their reputation as "brain juice" (3). Perceiving them as brain juice, students may show a tendency to use these drugs without a prescription (6). Half of non-prescribed drug users take them to complete school or work assignments and for entertainment. The route of administration depends on the desired effect, availability, and environment (7). According to the National Survey of Drug Use and Health, 1.5% of adolescents aged between 12 and 17 report using non-prescribed stimulants (8). The peak age of non-prescribed stimulant use has been recorded as 16 years (8). Additionally, 35% of college students reported using stimulants prior to college entrance (8).



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Students who started using non-prescribed stimulants before college were reported to be more likely to use them via non-oral routes and have worse health than those who started using non-prescribed stimulants at college (8). Informing students about effective study techniques might not be very beneficial since the students that tend to misuse these stimulants are appeared to implement study strategies on a regular basis (9). However, users expressed that stimulants help them "be competitive" and maintain a certain level in their field. Fear of losing their standards seems to be a great motivation for stimulant use (9). While academic purposes seem like the primary reason for non-prescribed stimulant use, studies show that other motivations include increasing the effect of alcohol, partying, and socializing longer (10). Additionally, amphetamines are used for enhancing physical performance, and these drugs are categorized as "doping" and fall under bans (5). Because of their affect on dopamine receptors, such drugs can be addictive (11). CNS stimulants may increase the levels of certain chemicals, alter vital signs, and cause changes in electroencephalogram (EEG) patterns (1).

An electroencephalogram is a device that measures the electrical activity of the brain. It was discovered in 1875 by Richard Caton, and Hans Berger made the first recording of EEG 50 years later (12). EEG is used for measuring the electrical potentials produced by neurons under the cerebral cortex. These measurements are made by electrodes that are positioned around the scalp and sometimes other parts of the head. These recordings are made based on a reference electrode (12).

Electrical activity is mainly generated by pyramidal cell bodies that are located in the third and fifth layers of the cerebral cortex. Secondary to this activity, excitatory and/or inhibitory postsynaptic potentials (EPSP/IPSP) are produced with the help of neurotransmitters. In a certain cortical region, EPSP and IPSP create an electric field with positive and negative poles, and that is recorded by EEG (13).

The normal EEG is diverse, with a wide range of variability (13). Pathologies may appear differently in the EEG, and these patterns may be altered by the intake of stimulants (14). Frequencies that are recorded by the EEG are important for describing the pathology since different waves are involved in different states and pathologies (15). Waves are named in terms of their frequencies; waves with a frequency of 1-3 Hz are delta waves, 4-7 Hz are theta waves, 8-12 Hz are alpha waves, and 13 Hz and over are beta waves (12, 15). Although gamma waves with frequencies over 25 Hz are not commonly recorded, they can be encountered during intracranial recordings. Gamma waves of 25-70 Hz are called low gamma, and waves over 70 Hz are high gamma waves (15). Frequencies over 100 Hz are generally referred to as ripples, and they can be seen in EEGs with epileptiform activities (15).

This review aims to show the epidemiology, mechanism of action, addictive aspect, EEG changes, and long-term memory effects of caffeine, methylphenidate, and modafinil use among students.

## CAFFEINE

### Epidemiology

According to a survey of 37602 people from different age groups in the United States (US) 85% of the people consume at least one cup of caffeine-containing beverage per day (16). Coffee is the main source of caffeine in all age groups (16). In another study involving 1248 university students in the US, it was revealed that 92% of the students consume caffeine in various forms. The two most common reasons for caffeine consumption are caffeine's effect on feeling awake and liking the taste of caffeine (17). Caffeine consumption was also common among high school students in Delhi, India (18). Of the 300 high school students, 291 of them regularly consumed caffeine (18).

In a survey conducted on tertiary students in New Zealand, it was determined that 99.1% of the participants consume caffeine (19). These students consume products involving caffeine, such as tea and chocolate, for their taste and coffee to stay awake (19).

### Mechanism of Action

The blood level of caffeine peaks approximately 1 hour after oral consumption (20). Almost all caffeine is metabolized in the liver by the CYP1A2 isoenzyme (21, 22). Its half-life is 3-5 hours, and it can easily cross the blood-brain barrier (21). Its excitatory effect on the brain starts when caffeine inhibits the non-specific inhibitory A1 and A2 adenosine receptors (23). The effects of caffeine vary depending on age, gender, and demographics (24). This difference is thought to be caused by the variations in CYP1A2 enzyme activity of the individuals (22).

### Effects on Memory and Attention

Caffeine, the most widely used psychostimulant, has important effects on memory and attention (25). Kahathuduwa et al. (26) stated that caffeine significantly improved the cognitive simple visual reaction time. It also has a positive effect on sustained attention and long-term memory as a cognitive enhancer (27, 28). In addition, it has been shown to improve memory performance in people who are sleep-deprived or elderly (29). The fact that it increases concentration in sleep-deprived people confirms that it may have a stimulant effect, but a statistically significant result was not found in healthy people, which makes it difficult to accept caffeine as a pure stimulant (30). Additionally, it is thought to reduce the impairment of memory in neurological diseases such as Alzheimer's (29).

### Effects on EEG

The electroencephalograms of ten healthy young men were recorded before and after caffeine consumption in a randomized, controlled, double-blind trial (31). According to the EEG results, it was determined that the amplitude in the fronto-parieto-occipital and central electrodes were reduced after caffeine intake (31).

In another study, EEG waves were measured during the caffeine withdrawal period, and it was found that there was a significant increase in the amplitude of alpha and theta waves during this period (32). In the clinical trial conducted by Sigmon et al. (33), it was observed that caffeine increased the amplitude of theta waves in the EEG and decreased the amplitude of the beta 2 (25-40 Hz) waves in the acute withdrawal period. Additionally, the acute effects of caffeine were detected in several parameters, such as cerebral blood flow and EEG, while the effect of chronic caffeine consumption was only seen in beta 2 waves in the EEG (33).

Another study revealed that people who took citicoline-caffeine drinks exhibited higher attention and learning speeds, considering their EEG results (34). Citicoline, which is formed by the combination of cytidine and choline, has a positive effect on the cognitive functions of the brain in addition to the effects of caffeine on attention and neurocognitive functionality (34).

In addition to the effect of caffeine on EEG, it can be said that caffeine reduces the reaction time and the number of mistakes made in event-related potentials (ERP) (35). In this case, it is seen that the stimulating effect of caffeine is also supported by the ERP (35).

#### **Caffeinated Energy Drinks: An Important Health Issue for Adolescents**

Energy drinks are high-caffeine beverages formulated to improve mental and physical stimulation (36). In recent years, they have become very popular among adolescents, despite their various side effects (37). Caffeine intoxication is one of the main side effects of energy drinks (36). It has been determined that side effects are more common in those who drink more than 5-7 energy drinks per week (36).

According to a study, 67% of high school students consume these drinks to stay awake, 65% to increase their energy, and 54% to drink with alcohol at a party (38). As side effects, headaches were reported in 22% of young people, and tachycardia was observed in 19% (38).

#### **Addiction**

Although it is not recommended for children and adolescents to consume caffeine, up to 6 mg/kg of daily consumption may be suggested for young adults because of its positive effects (20). However, consuming more than 300 mg of caffeine at a time or more than 1000 mg daily may lead to caffeine intoxication, which may cause arrhythmia, tachycardia, muscle tremors, or psychomotoric distress (20, 21).

Students under stress tend to consume more coffee, which increases the risk of developing caffeine addiction (39). Especially among senior students, excessive coffee intake has been associated with anxiety and depression symptoms (40). A randomized controlled trial also found that caffeine delays rapid eye movement (REM) sleep (40).

## **METHYLPHENIDATE**

### **Epidemiology**

Methylphenidate is one of the primary drugs for the treatment of ADHD, and it is used as a secondary treatment for narcolepsy (41, 42). It was proven that it is used by the majority of patients diagnosed with ADHD (41). Male gender and comorbidity of neuropsychiatric disorders increase the tendency to use methylphenidate (43). Additionally, males tend to misuse cognitive enhancers more (44). Hunter et al. (45) examined the prescription trends in 2009-2018 and reported that methylphenidate accounts for 15% of the 356,548 pediatric psychotropic drug prescriptions. In the US, non-medical utilization of stimulants on prescription is common and increasing among college students, as is the consumption of methylphenidate in the world (44). Increased awareness of ADHD and extended treatment duration may have caused an increase in the prescription of methylphenidate (44).

### **Mechanism of Action**

Methylphenidate interrupts catecholamine metabolism, stops the reuptake of norepinephrine and dopamine in synapses, and enhances the stimulant effect on the CNS, mainly at the prefrontal cortex (11). Norepinephrine and dopamine transporters have particularly high affinities for methylphenidate. It blocks dopamine and norepinephrine transporters by competing with catecholamines, resulting in higher concentrations of dopamine and norepinephrine (11). In addition to the stimulation, because of the impact on dopamine and other catecholamine mechanisms, it increases the motivational willingness of the individual (11). It gets metabolized primarily in the liver by re-esterification to ritalinic acid, and 78-98% of the drug is excreted by urination (46).

### **Effects on Memory and Attention**

In healthy subjects, methylphenidate increases attention and cognition by increasing dopamine and norepinephrine in many parts of the CNS, such as the dorsolateral prefrontal cortex, posterior parietal cortex, and striatum of the subcortical basal ganglia (47). Baseline working memory capacity is a parameter that is positively correlated with the striatal synthesis of dopamine (48). Van der Schaaf et al. (48) reported that methylphenidate improves the performance of cognitive tasks in high-working memory subjects or impairs it in low-working memory subjects.

Repantis et al. (27) stated that methylphenidate affects long-term declarative memory positively. Another study by Rostami Kandroodi et al. (49) showed that the effects of methylphenidate depend on the individual differences of the subjects, the drug improves cognitive task performance while impairing learning in participants with higher-working memory capacity. It has also been shown that language processing was better with lower-working memory capacity after methylphenidate was administered (50).

### Effects on EEG

In acute usage, it is found that the alpha and beta activities increase in the frontal areas, and the delta and theta activities decrease in the parieto-occipital and occipital areas (51). It is also reported that P3, an evoked response potential identification component on EEG, can be used to differentiate people with ADHD from healthy individuals for visual and auditory tasks by ERP technique (52). It is also proven that the theta/beta ratio was more sensitive in continuous performance tests in parieto-occipital areas of the right hemisphere when methylphenidate was administered (52).

### Addiction

Based on clinical experience, a clinical trial stated that methylphenidate is said to be beneficial for substitution therapy for cocaine (53). Duka et al. (54) reported that genetic variants of the *GABRA2* gene may be associated with methylphenidate addiction, which may explain why some people are more prone to addiction. In another study, it was suggested that a combination of fluoxetine and methylphenidate mimics cocaine activity both on behavioral effects and gene regulation in the striatum, indicating a potential risk of substance abuse (55). Recently, misuse of pharmaceutical cognitive drugs has increased, with the prevalence varying from 6% to 20% among university students (6). Several cases of toxicity and fatalities have been reported due to methylphenidate misuse, and its effects on the heart, such as palpitations, tachycardia, hypertension, and endocarditis, seem to be important for methylphenidate analogs' toxicity (56). It is suggested that high-risk groups, such as students and addicts, should be educated about the dangers and consequences of using such substances (56). From a legal perspective, methylphenidate and its analogs may be systematically controlled (56).

## MODAFINIL

### Epidemiology

Modafinil, a stimulant that is used to treat ADHD, is also a wakefulness-promoting agent used for the treatment of excessive daytime sleepiness associated with disorders such as narcolepsy, sleep apnea, and shift-work sleep disorder. Modafinil was found to improve attention and memory while helping to maintain wakefulness in well-rested individuals (57). However, some studies note that, particularly in healthy, non-sleep-deprived college students, modafinil does not have positive effects on sustaining studying except for non-demanding tasks (58). This evidence points out that modafinil has limited potential as a cognitive enhancer if the individual is not sleep-deprived (59).

In an online poll managed by Nature, 20% of the 1400 responding readers reported non-medical use of modafinil or beta-blockers, 62% reported taking modafinil, and 44% reported taking modafinil for non-medical reasons (57). The main reasons for the non-medical use of modafinil were improving focus,

preventing jetlag, and overcoming sleep deficiency (57). It is also known that modafinil is misused by college students for academic purposes (57). The indirect evidence for the misuse of modafinil can also be proved by comparing the sale numbers of modafinil to the patients suffering from the disorders from which these substances are used (57). Modafinil is also used by military personnel during long missions, as depicted in the Memorandum of the United States Air Force "Modafinil and management of aircrew fatigue" (2<sup>nd</sup> December 2003), which approves the use of modafinil for missions of great duration (57).

### Mechanism of Action

Modafinil is a stimulant that is better tolerated than conventional stimulants such as methylphenidate, which has a selective site of action in the brain (60). Modafinil is associated with improved attention, vigilance, memory, and learning as it affects the frontal lobe (61). One study shows that modafinil affects cortical areas of the frontal lobe and has minor activity in subcortical regions. It increases extracellular catecholamine levels through the inhibition of dopamine and noradrenaline transporters like methylphenidate and indirectly activates the hypocretinergic system. However, modafinil's exact mechanism is not yet clear. It is important to note that modafinil is also believed to affect other neurotransmitter systems, including serotonin, histamine, and glutamate pathways (62, 63).

In healthy male volunteers, the duration of modafinil activity was investigated in two double-anonymous crossover studies (64). These studies indicated that modafinil has a long duration of action while predominantly exhibiting alerting properties from dopaminergic activity. The mode of action was explored by using a model about the relationship between total sleep time and duration of REM sleep. While the model showed no evidence of direct suppression of REM sleep, it revealed that the increase in REM sleep was because of the alerting activity of dopaminergic activity. Enhanced performance with modafinil during overnight work varied with dose. However, when the next-day performance was evaluated, cognitive enhancement was the least at the highest dose (300 mg) due to the disturbance of prior sleep (64).

### Effects on Sleep, Memory, and Attention

According to a systematic review, modafinil helps healthy individuals maintain wakefulness and improve memory after one night of sleep deprivation (63). Another study showed that the administration of psychotropic medications such as modafinil to long-term cocaine users may be beneficial in improving memory (65). For non-sleep-deprived healthy individuals, modafinil may have stimulating effects in maintaining relatively difficult and monotone tasks and improving memory (63). In a study, modafinil significantly enhanced performance on digit span tests, visual pattern recognition memory, spatial planning, and stop-signal reaction time. There were no significant effects of the drug on spatial memory span, spatial working memory, rapid visual information processing, or attentional set-shifting (66).

### Effects on EEG

Modafinil is a wakefulness-promoting agent that affects hypothalamic structures involved in the homeostatic and circadian regulation of vigilance. In the case of sleep deprivation, the administration of modafinil reduces the need for recovery sleep and decreases the rebound in EEG slow wave activity (67). Modafinil administration during continuous positive airway pressure (CPAP) withdrawal increased awake EEG activation, which is associated with an improvement in neurocognitive performance. This study presents supporting neurophysiological evidence that modafinil may be a potential short-term treatment option during acute CPAP withdrawal (68).

### Addiction

Modafinil was originally indicated as a cognitive enhancer that has a low risk of addiction with a few side effects. It is becoming clearer that the drug is acting on dopaminergic transmission, and, like other psychostimulants, it has a risk of addiction. Yet, the long-term effects are still not completely explored (69). It has been reported that modafinil and armodafinil, which is an oral non-amphetamine wake-promoting agent, improve excessive daytime sleepiness symptoms and have little abuse potential (70).

Dextroamphetamine is authorized for use by the aircrews of all US military services, but its potential for abuse and subsequent addiction is of concern. Finding an alternative stimulant like modafinil, which has a low affinity for dopamine uptake binding sites, would be beneficial, as it does not have the potential for abuse, unlike dextroamphetamine (71). Another study suggests that modafinil does not have a high potential for abuse in cocaine abusers. With the increased cocaine abstinence and reduced craving results in some studies, it may be a promising medication (72).

### CONCLUSION

Students may use different stimulants for several reasons, such as staying awake to study, increasing alertness to complete assignments, or for recreational purposes (73). With a lifetime prevalence of 6.9% among American college students, stimulant use seems to be perceived as a "physically harmless" and "morally acceptable" act (42, 74). Students are often inclined to justify the use of stimulants by comparing them to synthetic drugs, expressing that they are using stimulants to achieve better grades or study more effectively, and arguing that no physical or cognitive side effects exist (74). One such substance, methylphenidate, is widely used for ADHD and has a high potential for abuse (75). A study by Barrett et al. (75) reported that while 70% of methylphenidate abusers used the substance for recreational purposes, the remaining 30% used it solely for academic purposes. This may challenge the justifications regarding stimulant use to increase academic performance. In addition, since many intoxications were reported due to the misuse of methylphenidate, high-risk populations, such as students

and current users, should be educated about the negative side effects of such drugs (56).

Increased delta and theta activity in the EEG is generally linked to inattentiveness and poor task performance. A study by Lubar et al. (76) revealed that increased beta activity was correlated with increased delta and theta activity when participants were taking methylphenidate, which contrasts with the positive relationship between improved task performance and increased beta activity. However, it does align with previous reports suggesting that long-term use of methylphenidate may not lead to significant cognitive or academic improvements (57). It is possible that increased slow activity while under the influence of methylphenidate impedes cognitive processing, despite reducing hyperactive behavior in individuals with ADHD (57).

The effects of another cognitive enhancer, modafinil, have been found to be inconsistent and varying among sleep-deprived and non-sleep-deprived individuals (59). Fernández et al. (58) reported that non-sleep-deprived, healthy students do not benefit from modafinil, which is often used for its enhancing effects on studying and focus. Since no significant difference between 100 mg and 200 mg doses of modafinil was reported and the safety of the drug remains unclear in healthy and non-sleep-deprived individuals, its effectiveness as a cognitive enhancer seems to be lacking (59). Modafinil reduces sleepiness and attenuates theta wave activity in the EEG during wakefulness. However, it does not affect EEG activity during REM sleep. Furthermore, it does not alter slow-wave sleep or slow-wave activity in the EEG during non-REM (NREM) sleep following sleep deprivation, suggesting that modafinil does not interfere with the compensatory increase in NREM sleep after prolonged wakefulness (60).

Caffeine is the most widely used stimulant in all age groups, and its benefits include a longer attention span, enhanced long-term memory, and improved visual reaction time (17, 27-29). Despite its many favorable effects, taking more than 1000 mg daily may lead to caffeine intoxication, causing tachycardia and muscle tremors. Since caffeine is a well-studied food component and is consumed by 85% of the US population daily, individuals should be well-informed about the benefits, ideal doses, and unfavorable side effects of this substance (17). It has been reported that headaches during caffeine withdrawal and an increase in alpha and theta amplitudes in the EEG are a result of cerebral vasodilation. However, caffeine intake seems to reverse these effects by causing vasoconstriction (32). Interestingly, a study by van Oosterhout (77) revealed that caffeine may have no effects on the alpha frequency amplitudes in resting-state EEG, highlighting the need for more studies in the area. It would perhaps be a correct approach to investigate whether different doses of caffeine intake affect the amplitude of the alpha waves.

Since many stimulants are readily accessible to many individuals, such substances have the potential to be misused. Although it is important to monitor the prescription and distribution of cognitive-enhancing drugs, it is crucial for individuals who use cognitive enhancers and those contemplating doing so to be

fully aware of the benefits, risks, side effects, and unfavorable outcomes of using such substances.

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